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REVIEW

Nuclear Medicine Techniques in the Diagnosis of Cardiac Amyloidosis

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Abstract: Cardiac amyloidosis (CA) represents the accumulation and deposition of misfolded protein fibrils in the myocardium, resulting in progressive restrictive cardiomyopathy. Light chain (AL) and transthyretin (TTR) amyloidosis are the most common types of CA. While endomyocardial biopsy remains the gold standard for diagnosing cardiac amyloidosis, its invasive nature and associated risk of complications have led to increased reliance on clinical suspicion and noninvasive imaging modalities as alternative diagnostic tools. Over the last decade, radionuclide imaging studies have become a widely accepted tool in diagnosing ATTR CA, whereas its diagnostic utility in AL CA detection remains limited. Recent advances in PET-CT radiopharmaceuticals have further expanded the potential of nuclear imaging as a comprehensive tool for diagnosis, prognostication, and therapy monitoring. This literature review appraises the current applications of nuclear imaging in the clinical management of cardiac amyloidosis.

Keywords: Cardiac amyloidosis; Transthyretin amyloidosis; Light-chain amyloidosis; Radiolabeled bisphosphonates imaging; Amyloid-specific PET tracers; Non-invasive cardiac imaging

INTRODUCTION

Amyloidosis is a heterogeneous systemic disease characterized by the aggregation and extracellular deposition of misfolded protein fibrils in various tissues and organs [1]. The term 'amyloid', derived from the Greek άmylon and Latin amylum – both meaning 'starch', in reference to its iodine staining properties – was first introduced into the scientific literature in the 19th century to describe iodine-positive deposits observed in the brains of patients with dementia [2]. Cardiac amyloidosis (CA) refers to myocardial infiltration by amyloid fibrils, leading to progressive restrictive cardiomyopathy and associated cardiovascular manifestations. Although the type of CA cannot be differentiated based on patterns of deposition, there seems to be a prevalence of diffuse, pericellular, endocardial, and arterial or arteriolar deposits in AL amyloidosis, with nodular deposits in TTR amyloidosis [3].

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The most frequent clinical forms – accounting for more than 95% of cases – are light-chain (AL) and transthyretin (TTR) amyloidosis [3]. AL (or primary) amyloidosis results from the deposition of misfolded immunoglobulin light chains, aggregated as amyloid fibril precursors. These last can damage the tissues directly – through their

proteotoxicity – or form stable fibrils – causing organ damage through impaired histological architecture [2]. TTR amyloidosis is characterized by pathological deposits of transthyretin, a normally occurring protein used in transportation of thyroid hormones and retinol-binding [4]. Wild-type transthyretin amyloidosis (ATTRwt) – formerly known as senile systemic amyloidosis – is an age-related form of cardiac amyloidosis, most often presenting in the seventh decade of life, with a marked male predominance [2,5]. In contrast, variant transthyretin amyloidosis (ATTRv), which is inherited in a dominant autonomic fashion with incomplete dominance, may present as early as the third decade of life, depending on the specific mutation [2,3,5].

With divergent prognoses, treatment strategies, and therapeutic responses, early and precise diagnosis of the distinct forms of cardiac amyloidosis is therefore essential to guide appropriate and timely management. While endomyocardial biopsy remains the gold standard for diagnosing cardiac amyloidosis, its invasive nature and associated risk of complications have led to increased reliance on clinical suspicion and noninvasive imaging modalities as alternative diagnostic tools [4,6].

This paper aims to present current nuclear imaging modalities of diagnosing cardiac amyloidosis and to synthesize recent evidence regarding their prognostic significance and role in evaluating therapeutic response in patients with CA.

CLINICAL SPECTRUM, BIOMARKERS, AND CONVENTIONAL IMAGING

Clinical manifestations

Cardiac amyloidosis is associated with a spectrum of clinical manifestations reflecting the gradual myocardial infiltration and consequent restrictive physiology. Amyloid infiltration leads to progressive thickening of the atrial and ventricular walls, culminating in diastolic dysfunction and heart failure (HF) – often with preserved ejection fraction. Systolic dysfunction typically occurs in the later stages of the disease. While atrioventricular block and tachyarrhythmias also become increasingly clinically apparent as the disease advances, common cardiac symptoms include fatigue, shortness of breath, and syncope [2,3].

AL amyloidosis, caused by clonal plasma cell dyscrasias, typically presents as a multisystemic disease, most frequently involving the heart and kidneys (60-70%), but also the liver (15%) and peripheral nerves (10%) [3]. The amyloidotic heart shows symmetrical increase in biventricular wall thickness (pseudohypertrophy) with markedly increase LV stiffness and filling pressures – in the presence of nondilated or small ventricles [2]. Due to restrictive cardiomyopathy and fibril proteotoxicity, patients with AL amyloidosis can present with dyspnea, fatigue, arrhythmias, severe fluid retention, hepatomegaly and ascites [1,2]. Circulating light chains exert direct cardiotoxic effects, contributing to rapid disease progression and disproportionately elevated cardiac biomarkers relative to amyloid burden [3]. Late-stage diagnosis, when cardiac and renal damage is advanced, correlates with a poor survival – measured in weeks [1,3].

ATTR amyloidosis also presents with a cardiac-dominant phenotype – manifesting as left ventricular hypertrophy (LVH) and HF [5] – particularly in the wild-type form (ATTRwt), which affects elderly men and follows a slow progression. Early extracardiac manifestations, such as bilateral carpal tunnel syndrome, lumbar stenosis or biceps tendon rupture, may precede cardiac symptoms by several years [1,3]. Severe aortic stenosis (SA) has been associated with cardiac amyloidosis, especially in the ATTR variant, as amyloid fibril deposition within valvular tissue contributes to leaflet thickening and progressive stenosis. The coexistence of CA and SA has been reported to have a poorer prognosis; therefore, concomitant diagnosis is essential in guiding appropriate therapeutic management [7]. ATTRv manifestations vary by mutation: Val122Ile leads to predominant cardiac involvement, while Val30Met causes early-onset neuropathy and Thr60Ala produces mixed features [3]. Late-onset ATTRv and ATTRwt share similar cardiac presentations and fibril compositions, often involving both full-length and fragmented transthyretin [2].

Serum biomarkers

When cardiac amyloidosis is suspected, initial evaluation should include serum measurements of N-terminal pro-B-type natriuretic peptide (NT-proBNP), troponin, creatinine and free light chains, along with calculation of estimated glomerular filtration rate (eGFR). A study by Ionescu et al. [8] found the burden of cardiac amyloidosis on eGFR to be more pronounced in ATTR patients compared to AL, regardless of the method used (either by MDRD formula or the Cockcroft-Gault equation).

Assessment of serum and urinary free light chains should be performed to aid the differentiation between ATTR and AL amyloidosis. An abnormal kappa-to-lambda free light chain ratio may be indicative of AL amyloidosis. For further evaluation of the differential diagnosis, bone marrow biopsy is recommended to distinguish between AL amyloidosis and multiple myeloma [2].

Electrocardiography

As one of the simplest yet highly informative diagnostic tools, electrocardiography (ECG) can reveal several ‘red flags’ – particularly when interpreted in conjunction with imaging findings – allowing for a refined prognosis and stratification. ECG appearances suggestive of cardiac amyloidosis are defined by a pseudoinfarction pattern and disparity between the LV wall thickness and low QRS voltage. Due to myocardial infiltration of non-conductive material, the direct proportionality correlation between QRS voltages and LV mass is therefore abolished. The pseudoinfarction pattern consists of the presence of Q waves measuring at least 1mV in at least 2 contiguous leads, in the absence of ischemic heart disease and/or regional kinetic abnormalities of the LV [2,5]. In AL CA, low

peripheral voltage is more common due to proteotoxicity of misfolded light chains, whereas ATTR CA presents more frequently with conduction disease (incomplete or complete bundle branch block), arrhythmias (atrial flutter or fibrillation) and bradycardia [2,3].

Echocardiography

Echocardiography signs suggestive for cardiac amyloidosis consist of increased LV wall thickness (>12 mm) with relative apical sparing ("cherry on top"), low tissue doppler velocities, restrictive filling pattern, increased biatrial volume, atrial septal thickening (>6 mm) and pericardial effusion. LV wall thickness is usually more pronounced in ATTR CA (>15 mm), which also presents more commonly with concomitant aortic stenosis [3,9]. Combining ECG and echocardiographic findings has been shown to provide higher diagnostic accuracy, with 91% sensitivity and 89% specificity in cases with a ratio<0.4 between R-wave amplitude in lead I and posterior wall thickness [2].

Cardiac magnetic resonance (CMR)

Cardiac magnetic resonance imaging, particularly late gadolinium enhancement (LGE) and T1 mapping techniques, allows for noninvasive tissue characterization, therefore aiding the differential diagnosis of cardiomyopathies with hypertrophic phenotypes by detecting amyloid deposits in the myocardium [9]. Morphofunctional quantification reveals concentric and symmetric left ventricular hypertrophy with preserved ejection fraction but reduced indexed stroke volume – often in the context of diastolic dysfunction. Associated findings include thickened valves, left atrial appendage thrombi, atrial enlargement, interatrial septum hypertrophy and mild pericardial and pleural effusions. Increased native T1 mapping is particularly sensitive for early myocardial involvement, often detecting abnormalities before late LGE becomes apparent. Especially during early to intermediate contrast phases, LGE typically demonstrates diffuse subendocardial enhancement in a non-coronary distribution with relative apical sparing. In advanced stages of CA, transmural or intramyocardial, patchy enhancement may be observed, extending into the right ventricle or atria. Characteristic features include myocardial nulling preceding blood pool nulling and early blood pool darkening. Additionally, elevated extracellular volume (commonly>40%) serves as an indirect marker of amyloid burden and correlates with disease severity and prognosis [2,10].

NUCLEAR MEDICINE IMAGING IN CARDIAC AMYLOIDOSIS

Radiopharmaceuticals

Non-amyloid specific radiopharmaceuticals currently used in cardiac scintigraphy are bone-avid radiotracers. These radiopharmaceuticals are labelled with 99mTechnetium: 99mTc-diphosphono-1,2-propanodicarboxylic acid ([99mTc]Tc-DPD), 99mTc-pyrophosphate ([99mTc]Tc-PYP) or 99mTc-hydroxymethylene diphosphonate ([99mTc]Tc-HMDP) [11]. A comprehensive study by Gilmore et al. [12] has shown high specificity and sensitivity of 99mTc radiotracers for TTR amyloidosis, which correlates with negative monoclonal proteins in blood and/or urine samples. It is not yet fully understood why phosphonate compounds accumulate in cardiac tissue at the sites of amyloid deposition. It is hypothesised that this is because amyloid fibril deposits have a higher concentration of microcalcifications in the cardiac TTR, together with slow disease progression and therefore the potential for greater accumulation of deposits in the myocardium and/or other systemic structures. [4,13,14]

A study conducted by Park et al. [15] comparing 99mTc-PYP and 99mTc-DPD showed that the latter may be more useful in evaluating the severity of the disease. They found a more significant relationship between uptake and visual grading, as well as with biological parameters in [99mTc]Tc-DPD scans. Further studies are necessary in order to formulate a proper conclusion.

Quarta et al. [16], in their study of [99mTc]Tc-DPD uptake in AL CA, found a high percentage of patients with bone tracer uptake, almost a third of them with moderate cardiac uptake. This emphasizes the necessity of serological exclusion of plasma cell dyscrasia in case of bone tracer uptake in the myocardial tissue.

There has been a growing interest in recent years for the applicability of amyloid specific radiotracers, used in positron emission tomography – computed tomography (PET/PET-CT) studies in the diagnosis of cardiac amyloidosis [17]. Their primary use is for detection of Alzheimer disease [18]. These radiotracers bind directly to the beta amyloid, thus identifying any other systemic sites of amyloid aggregates. They are not yet approved for clinical use in diagnosis of CA but have shown promising results [19]. Rosengren et al. [20] were able to show high accuracy of 11C-labeled Pittsburgh compound B ([11C]PiB) in the detection of AL CA. Patients with documented systemic amyloidosis and only cardiac wall thickness also had [11C]PiB uptake on PET-CT scans, suggesting a prospective use of it in preliminary stages of the disease. Furthermore, Choi et al. [21] showed that PET-CT with [11C]PiB is a reliable independent factor for 1 year survival in patients with AL CA, alongside other established bio-indicators. The survival rate after 1 year in their 35 patients with [11C]PiB uptake was a little over 50%. Lee et al. [22] determined that PET scans with [11C]PiB are useful in quantifying the degree of amyloid burden by grade of uptake. Their prospective study reflected the usefulness of [11C]PiB in predicting overall outcome. A reduction in the uptake after treatment was observed in a small number of patients, raising the possibility of [11C]PiB PET as a non-invasive tool of assessing treatment response.

Similarly, Genovesi et al. [23] tested the feasibility of [18F]Florbetaben PET-CT for detection of AL amyloidosis. Their results showed that it may be able to detect light chain amyloid burden and to discriminate between forms of CA and other restrictive

cardiomyopathies. Along with a previous pilot study by Law et al. [24], both may endorse the use of [18F]Florbetaben as a non-invasive imaging technique to diagnose AL amyloidosis, yet further studies are necessary. It may represent an aid to scintigraphy, which cannot discriminate from other than TTR cardiac amyloidosis.

Apart from the amyloid-specific radiotracers, Wang et al. [25] showed the potential use of 68Ga-labeled Fibroblast Activation Protein Inhibitor ([68Ga]FAPI) PET-CT imaging for the diagnosis of AL CA, due to fibroblastic activity – a possible new instrument in heart failure and its cardiac implications [26].

Radionuclide imaging techniques

Planar acquisition

Interpretation of the cardiac planar images is based on a relatively simple visual scoring and a semiquantitative analysis. The visual grade consists of the Perugini score (Table 1), comparing the intensity of the cardiac uptake with rib cage uptake, and is more useful in case of [99mTc]Tc-DPD or [99mTc]Tc-HMDP [13, 27]. Grade 0 represents no cardiac uptake of the 99mTc radiotracer – and normal uptake of the ribs – being considered negative for CA. Grade 1 – equivocal for the diagnosis of ATTR amyloidosis – consists of mild cardiac uptake, less than rib uptake. Grade 2 represents cardiac uptake of the radiotracers equal to the rib uptake, while Grade 3 translates to a cardiac uptake greater than that of the rib cage. Grades 2 and 3 on planar studies are considered ATTR positive – after the exclusion of plasmatic dyscrasia [28].

Table 1: Visual grading system of myocardial radiotracer uptake on bone scintigraphy according to the Perugini score

Perugini score	Cardiac uptake
Grade 0	absent
Grade 1	cardiac uptake < rib uptake
Grade 2	cardiac uptake = rib uptake
Grade 3	cardiac uptake > rib uptake

Semiquantitative indicators consist of several methods of evaluation, including the heart-to-contralateral ratio (H/CL), most valuable in the case of bone scintigraphy with [99mTc]Tc-PYP [13]. The H/CL measures the ratio between the counts in the two regions of interest (ROI) – the heart and the contralateral lung. With a value greater than 1.5 on one-hour acquisitions, in correlation with a Perugini score of 2 or 3, the cardiac study is highly suggestive of TTR cardiac amyloidosis [28]. However, in cases where the Perugini score is classified as grade 1, histological confirmation of amyloid deposits (potentially located in the extracardiac tissues) is required to establish the diagnosis and determine the amyloid type [29].

The current standard time between injection and acquisition is between one (1h) and three hours (3h) [30]. Images at one hour have a higher sensitivity due to peak myocardial uptake, yet it is of higher specificity in the case of delayed images [17]. Saitou et al. [31] confirmed this remark by a comparison between planar acquisitions at 1h and 3h post-injection on radiolabeled bisphosphonate scans with [99mTc]Tc-PYP. Their study showed a higher specificity in planar 3h studies – results corroborated with single photon emission computed tomography with computed tomography (SPECT-CT). Moreover, a 3h scan can provide a more accurate diagnosis, as proven by their differences in positive predictive values (almost 80% after 3h versus 57% after 1h). Similarly, Nichols et al. [32] emphasized the advantages of using 3h planar and SPECT-CT images for diagnosis. Three-hour acquisitions are advantageous due to lesser blood pool activity and peak bone uptake [11].

SPECT and SPECT-CT

SPECT-CT, a hybrid imaging technique that evaluates function through SPECT and anatomy through CT, provides a useful three-dimensional assessment with the possibility of segmental evaluation and attenuation correction [13].

The visual scoring on planar images is a well-established and reliable method of analysis. Nevertheless, it is prone to misinterpretation because of blood pool activity, osseous uptake that overlaps the cardiac region or inexperience of the interpreter [30]. SPECT-CT images are able to confirm the diffuse left ventricular, biventricular, interventricular septum and/or atrial myocardial uptake of the radiotracers, highly suggestive of cardiac amyloidosis.

Quantification of cardiac uptake on SPECT-CT using standardized uptake values (SUV) was shown to have greater accuracy than visual assessment on planar-only acquisitions. SUV is a semiquantitative index that reflects the uptake of radiotracer in the tissue, but it has yet to be included in standard practice. It is the ratio between radioactivity in a region of interest (ROI) and the dose administered per the body weight of the patient. Kessler et al. [33] compared quantitative SPECT and SPECT-CT results with those obtained through Perugini score in suspected CA patients that underwent [99mTc]Tc-DPD scintigraphy. A value of SUVmax greater than 6.1 showed a

higher specificity for CA and particularly for ATTR type – where a 99% specificity value has been reported. Furthermore, in a study by Taha et al. [34], the use of SPECT-CT fusion was able to enhance diagnostic accuracy by adding the anatomical element of the low-dose CT in order to differentiate between myocardial and ventricular diffuse uptake (blood pool uptake). Scully et al. [35] showed that the use of SPECT-CT and SUV values offers a more accurate means of distinguishing between Perugini scores of 2 and 3.

PET-CT

PET-CT imaging can be a more precise tool in describing anatomical and functional characteristics of the disease. PET-CT scans offer more accurate quantifying methods of the biological and physiological processes through SUV values, retention index, target-to-background ratio, as well as visual grading [30]. Amyloid-binding PET radiotracers have accumulated a substantial amount of evidence; however, they are not yet licensed for clinical application in CA. Further investigations are needed to optimize acquisition procedures and validate results in broader groups. In contrast to bone-avid scintigraphy and SPECT radiotracers, PET radiopharmaceuticals have been explicitly designed to attach to the amyloid fibrils. Consequently, PET is the sole imaging modality that is unequivocally selective for amyloid deposits and highly selective for amyloid variants. Moreover, PET is capable of detecting ATTR CA, AL CA, as well as uncommon hereditary variants. Advancements in the quantification of myocardial uptake in both SPECT and PET have produced more detailed and consistent results, facilitating improvements in early diagnosis, risk stratification, and treatment response assessment [36].

DISCUSSION AND FUTURE PERSPECTIVES

Atrial and right ventricular uptake: a new perspective in radionuclide cardiac imaging

The diagnostic role of scintigraphy with bone-avid radiotracers in the diagnosis of CA – specifically of TTR form – is almost in all cases unequivocal [12,37]. However, their role in the prognosis of CA remains still unclear. Recent years' studies have focused on this perspective.

The amyloid burden can be easily identified in the left ventricle alone – yet in most cases, biventricular and/or atrial strain is present, leading to restrictive myopathy [3]. Two promising fields of research regarding the role of radionuclides in prevention and prognosis assessment are the increased uptake in the atrium and in the left ventricle on scintigraphy. Porcari et al. [38] studied the implications of right ventricular uptake of bone radiotracers on scintigraphy. Their results showed a biventricular uptake in 100% of their total of 1422 patients with TTR amyloidosis, identified on SPECT and inconsistently on planar “whole-body” images. It is known that right ventricle involvement in heart failure is linked to an unfavorable disease evolution [5]. This study [38] identified a diffuse right ventricle uptake in more than half of their patients, which was an independent mortality predictor.

Atrial involvement is a part of the onset of cardiac alterations [37]. It appears as part of global amyloidosis (AL or TTR) or as regional impairment of the atrial function due to pathological natriuretic peptide accumulation age related [39]. Hussain et al. [40] reported a high percentage of patients with TTR amyloidosis and atrial fibrillation (AF) to have atrial uptake on [99mTc]Tc-PYP planar images and SPECT-CT. Scintigraphy with 99mTc derivatives is unequivocally useful in assessing the ventricular uptake. Nonetheless, this study raised awareness for atrial implications – with or independent of that of ventricular – related to prevalent high-risk cardiovascular manifestations (AF, thrombi, pulmonary embolism).

National and International Guidelines

Adopting a uniform, standardized protocol, locally and internationally, for nuclear medicine studies for CA, would ensure the best accuracy of disease detection, thus improving the therapeutic approach and prognosis of the patient.

A recent study done by Stan et al. [41] showed the necessity of implementing national standardized protocols – including acquisition times and interpretation algorithms – for accurate reporting of CA scintigraphy studies.

CONCLUSION

As of today, nuclear medicine imaging studies represent a viable and reliable non-invasive imagistic method to diagnose cardiac amyloidosis. Furthermore, what was once an incurable disease with scarcely any treatment prospects is now more easily and promptly diagnosed with the courtesy of vast improvements in the field of radiopharmaceuticals used in cardiac nuclear imaging. While the diagnostic value of bone-avid radionuclides is unequivocal in TTR cardiac amyloidosis, novel indicators of their use in earlier stages or cardiac particularities (atrial or right ventricle uptake associated with unfavorable outcomes) are highlighted through recent studies, persuading specialists to study more this field. Furthermore, with promising results in cardiac imaging, PET may be considered and approved as a viable means of diagnosis, assessment of prognosis, and response to therapy.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. No artificial intelligence automatically generated text was inserted in this manuscript, and no image was previously published in another journal or is under consideration for publication elsewhere. This research received no external funding.

Authors' contribution

Conceptualization G.S.P.,M.M.M. and S.M.S..; methodology, G.S.P., L.E.M., M.G.; validation, D.M. and S.M.S.; data curation, D.M., G.S.P., M.M.M.; writing—original draft preparation, G.S.P, M.M.M, B.C.; writing—review and editing, L.E.M.,C.M., V.C.M..; supervision, S.M.S.; project administration, S.M.S..; All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

The study was conducted under the Declaration of Helsinki. The research was conducted under ethical guidelines and regulations, ensuring compliance with all necessary protocols.

Patient consent for publication

Not applicable .

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